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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,555	WANG, RONG-FU	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030128*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The election without traverse of Group I, claims 1-17 and 19-22, filed August 12, 2005 is acknowledged and has been entered.

2. The election of species of the invention of Group I, wherein said tumor antigen is NYO-ESO-1, filed August 12, 2005 is acknowledged and has been entered. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-17 and 19-22 are pending in the application and are currently subject to restriction.

Election/Restrictions

4. To the extent that the claims are directed a tumor antigen designated "TRP2", and to extent that the claims are directed to any of the "tumor antigens" disclosed as suitable for use in making and using the relevant compositions disclosed by U.S. Patent Application Publication No. 2004/0002455 A1, the corresponding different species of the claimed invention are rejoined with the elected species of the invention.

Information Disclosure Statement

5. The information disclosure filed January 28, 2003 has been considered. An initialed copy is enclosed.

Priority

6. Applicant's claim under 35 U.S.C. § 119(e) for benefit of the earlier filing date of U.S. Provisional Application Serial No. 60/268,687, filed February 15, 2001, is acknowledged.

However, claims 1-17 and 19-22 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

In particular, the provisional application fails to adequately describe a composition or vaccine comprising a member of a genus of "immune effector cells". Although the provisional application describes such compositions or vaccines comprising dendritic cells or immune cells, such as B cells (e.g., page 2, paragraph 1), it does not describe such compositions or vaccines comprising *effector* cells *per se*; accordingly, the scope of the disclosure set forth in the provisional application and the scope of the claims differ and therefore the provisional fails to provide a proper and sufficient description of the claimed invention.

Furthermore, the provisional application fails to adequately describe a composition or vaccine comprising a member of a genus of "antigens". Although the provisional application describes such compositions or vaccines comprising a tumor antigen, such as TRP2 (e.g., page 2, paragraph 1), it does not describe such compositions or vaccines comprising members of a broad genus of "antigens", particularly antigens not associated with tumors (e.g., an antigen associated with a viral disease).

Moreover, although the provisional application describes compositions or vaccines comprising cell-penetrating peptides covalently linked to a tumor antigen or fragment thereof, it does not appear to adequately describe such compositions or vaccines comprising cell-penetrating peptides "associated" with an antigen, since presumably the latter include compositions or vaccines comprising cell-penetrating peptides that are not covalently attached to the antigen, or not directly linked to the antigen. Again, the scope of the disclosure set forth in the provisional application and the scope of the claims differ and therefore the provisional fails to provide a proper and sufficient description of the claimed invention.

With regard to claim 4, the provisional application does not describe the claimed composition comprising an antigen comprising multiple T cell peptides from different antigens.

With regard to claims 6 and 20, the provisional application does not describe the claimed composition comprising a macrophage or a fibroblast.

With regard to claim 12, the provisional application does not describe the claimed invention comprising NYO-ESO-1.

With regard to claims 16 and 17, the provisional application does not describe the claimed composition comprising a cell-penetrating peptide and an antigen, wherein the antigen is housed within a vesicle, or more particularly an endosome in the immune effector system cell.

To receive benefit of the earlier filing date under 35 U.S.C. §§ 119(e) or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the pending claims is deemed the filing date of the instant application, namely February 15, 2002.

Drawings

7. The drawing set forth as Figure 1 is objected to because the figure depicts amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 6. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection

would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figure at page 6 of the specification to include sequence identification numbers.

Specification

8. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 1 are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 6. Furthermore, there are sequences depicted at page 38, paragraph [0109], page 40, paragraph [0116], and page 43, paragraph [0123], which are not identified; and despite the amendment filed September 22, 2004, there remain multiple sequences disclosed in the tables, which is still not identified by a sequence identification number.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

9. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Some examples of such improperly demarcated trademarks include Taxol™ (page 31, paragraph [00085]) and Fungizone™ (page 38, paragraph [0108]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

10. Claim 15 is objected to because of the inconsistent use of the term "cell penetration peptide", as opposed to "cell penetrating peptide". Appropriate correction is required.

11. Claim 16 is objected to because of the inconsistent use of the term "immune system cell", as opposed to ""immune effector cell". Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 3, 4, 11, 12, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 are vague and indefinite because the claim 3 is directed to the composition of claim 1, wherein said antigen is a molecule comprising "multiple T-cell peptides". What are the "T-cell peptides" to which the claims are directed? An antigen, such as a protein, is an intact molecule unto itself, which is not generally described as comprising multiple peptides, unless the protein is a fusion protein comprising multiple heterologous peptides derived from distinct proteins. According to claim 4, however, the antigen to which the claims are directed includes a molecule comprising multiple "T-cell peptides" *from the same tumor antigen*. Does the use of the term "multiple T-cell peptides" indicate that the antigenic molecule binds multiple T-cells? Does the term indicate that the antigenic molecule comprises a chemically conjugated oligomer or synthetic concatamer of the same or different peptides that bind one or more T-cells? While it is suggested that the subject matter that Applicant may actually regard as the invention is the composition of claim 1, wherein the antigen comprises multiple "T-cell epitopes" (i.e., MHC class I- or class II-restricted peptides of about 9 amino acids in length that bind the T-cell receptor displayed at the surface of T-cells, including, for example, cytotoxic T cells and helper T cells, which are naturally produced by cells, such as antigen-presenting cells, by degrading the otherwise intact protein from which they are derived), because of the non-conventionality of the terminology actually used to describe that subject matter, the skilled artisan would not be fairly apprised of the metes and bounds of that subject matter so as to permit determination of infringing and non-infringing subject matter in satisfaction of the requirements for particularity and clarity provided by 35 U.S.C. § 112, second paragraph.

Claims 11, 12, 13, and 14 are vague and indefinite because the use of laboratory designations, such as "TRP-2" and "CPP1" as the sole means of identifying the tumor antigen or cell-penetrating peptide to which the claims refer. The use of laboratory designations only to identify a particular peptide or polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct peptides and polypeptides. Furthermore, in this instance, the specification discloses that the term "TRP2" is used to identify two different proteins, namely mouse "TRP2" and human "TRP2" (see, e.g., page 10, paragraph [038]), and it

cannot be determined to which of these two proteins claims 11 and 12 are directed. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention are not particularly and distinctly claimed so as to permit the skilled artisan to determine infringing and non-infringing subject matter and thereby satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

This issue may be remedied by amending the claims to include the amino acid sequence of the tumor antigen to which the claims, since the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide. For example, claim 11 could be amended to recite reference to the sequence identification number identifying the amino acid sequence of "TRP2" as set forth in the Sequence Listing.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-17 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

The claims are drawn to a composition comprising a member of a genus of "immune effector cell". According to claim 6, for example, the genus of "immune

effector cells" to which the claims are directed includes mature dendritic cells, B cells, macrophages, and fibroblasts. However, a fibroblast is not an immune cell; moreover, a fibroblast is conventionally recognized as an "effector" cell. The specification defines the term "immune effector cell" as "any cell which is capable of eliciting a T cell response in an animal" (page 9, paragraph [0034]). Such a definition provides no limitations, as any cell (e.g., a breast cancer cell) is capable of eliciting a T cell response in an animal, especially if the cell is derived from a different animal. Accordingly, the claims are directed to a genus of cells having no particularly described or apparent structural or functional features; therefore the genus has not been adequately described so as to permit the skilled artisan to immediately envision, recognize or distinguish members of the genus from other cells and thereby satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph. Moreover, given these facts, it would not be apparent to the skilled artisan what constitutes or characterizes an "immune effector cell" that can be used in making and using the claimed invention, and therefore the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Furthermore, the claims are directed a genus of "cell penetrating peptides". At page 8, paragraph [0029], the specification defines the term "cell penetrating peptide" as "a peptide having the ability to transduce another peptide or protein into a cell *in vitro* and/or *in vivo*". While the specification describes multiple members of the genus of "cell penetrating peptides" to which the claims refer (e.g., page 11, paragraphs [0040] and [0041]), these polypeptides or peptides differ markedly in structure and function. For example, at page 8, paragraph [029], the specification discloses the genus includes members such as HIV Tat and fibroblast growth factor; two proteins that have no apparent structural relationship, and apart from having the purported common ability to "transduce another peptide or protein into a cell *in vitro* and/or *in vivo*" share no substantial functional relationship. Accordingly, the genus of "cell penetrating peptides" to which the claims are directed includes members that are structurally and functionally unrelated. As such, the skilled artisan could not to immediately envision, recognize or distinguish members of the genus from other peptides and polypeptides, and therefore

the instant disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of peptides and polypeptides having the ability to transduce another protein into a cell, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because, there may be, as there is in this instance, unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language that adequately describes members of the

genus of "immune effector cells" or members of the genus of "cell penetrating peptides". A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Again, the Federal Circuit decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit an activity of BMP-2 to achieve therapeutic effect, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). In particular, the claimed method depends upon finding "cell penetrating peptides", which have the ability to transduce another protein into a cell *in vitro* and/or *in vivo*; without such a peptide or polypeptide, it is impossible to practice the invention.

Although the skilled artisan could potentially identify peptides or polypeptides that the ability to transduce another protein into a cell *in vitro* and/or *in vivo* by screening peptides and polypeptides using an assay that measures their ability to do so, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its

enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of "cell penetrating peptides" to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a peptide or polypeptide that can be used in making the claimed invention.

16. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising a mature dendritic cell, which has been pulsed with a synthetic protein comprising a peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 14, wherein said peptide is covalently linked to an antigenic peptide, **does not reasonably provide enablement for** making and using a composition comprising an immune effector cell and a cell penetrating peptide, wherein said cell penetrating peptide is associated with an antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are directed to compositions comprising a member of a genus of "immune effector cells", but as explained above in the "written description" rejection, the genus of cells is not adequately defined, so as to permit the skilled artisan to recognize or distinguish the members of the genus from other cells. The specification describes the genus as inclusive of fibroblasts, which are not immune cells and are not conventionally described as "effector" cells. While the specification teaches compositions comprising mature dendritic cells, it does not teach the skilled artisan to identify other "immune effector cells", which are suitable for use in making the claimed invention, as the skilled artisan is given inadequate guidance and direction to recognize

or distinguish members of the genus of "immune effector cells", or select suitable cells for use in making the claimed compositions. Furthermore, the specification teaches while mature dendritic cells are suitable, immature dendritic cells are apparently not; see, e.g., Figure 3. Moreover, the specification teaches spleen cells are also not suitable for use in making the claimed invention. Since such immature dendritic cells and spleen cells are, or comprise conventional immune effector cells (e.g., B cells), it is not immediately apparent how suitable "immune effector cells", apart from mature dendritic cells are recognized or distinguished. Consequently, the skilled artisan cannot predict whether any given cell, including, for example, a fibroblast is suitable for use in making and using the claimed invention. For these reasons, the claimed invention could not be made without undue and unreasonable experimentation.

The claims are directed to compositions comprising a member of a genus of "cell penetrating peptides", which, as explained in the "written description" rejection above, are peptides capable of transducing another protein into a cell *in vitro* and/or *in vivo*, but which otherwise vary substantially in structure function. While the specification describes examples of such peptides, including in particular those that are described at page 11, it does not teach the structural features of such peptides and polypeptides that correlate with their common ability to transduce another protein into a cell *in vitro* and/or *in vivo*. Without such guidance and direction, the skilled artisan could not predict whether any given peptide or polypeptide is suitable for use in making the claimed invention, or whether any such peptide or polypeptide has the ability to transduce another protein into a cell *in vitro* and/or *in vivo*. As such the skilled artisan could not recognize or distinguish such peptides and polypeptides without empirically determining whether any given peptide or polypeptide has such an ability. Such testing would necessarily involve synthesizing different proteins comprising the amino acid sequences of a candidate "cell penetrating peptide" and an antigen and performing the sort of experiment used to generate the data depicted in Figure 1. Even if this methodology is fairly routine, given the size of the genus of antigens, the size of the genus of candidate "cell penetrating peptides", the unpredictable nature of the art, and the amount of

guidance, direction, and exemplification disclosed, the claimed invention could not be made without undue and unreasonable experimentation.

This position is supported by disclosures in the instant specification. For example, the specification discloses that a composition comprising dendritic cells pulsed with a synthetic protein comprising the amino acid sequences of an "irrelevant peptide" (i.e., "IR") and an antigenic fragment of the tumor antigen designated "TPR2" is incapable of eliciting an effective antitumor immune response in mice.

Broadly interpreted the claims are drawn to a composition comprising a "cell penetrating peptide" associated with antigen, but not necessarily a "cell penetrating peptide" that is covalently linked by a peptide bond to an antigen, such as the synthetic peptides that are exemplified in the specification. While the specification does not provide limiting guidance or direction as to how the "cell penetrating peptide" and the antigen are necessarily associated, it is presumed that the "cell penetrating peptide" and the "antigen" are not necessarily conjugated to one another, or perhaps not even bound to one another. The specification, however, does teach that a composition comprising dendritic cells pulsed with a "cell penetrating peptide" and an antigenic peptide is not effective to stimulate an antigen-specific immune response unless the "cell penetrating peptide" is physically linked by a peptide bond to the antigenic peptide; see, e.g., page 45, paragraph [0127]. Given this disclosure, the specification provides factual evidence suggesting that a "loose", non-covalent association of the "cell penetrating peptide" and the antigen is not sufficient; rather, the specification provides factual evidence that the composition must comprise "immune effector cells" that are pulsed with a synthetic protein comprising the amino acid sequence of the "cell penetrating peptide" adjoined to the amino acid sequence of the antigen. The skilled artisan cannot predict whether any other compositions encompassed by the claims, wherein the "cell penetrating peptide" and the antigen are merely "associated", as opposed to covalently linked by a peptide bond, are suitable for use in making and using the claimed invention. As such the breadth of the claims would serve merely as an invitation to the skilled artisan to further elaborate the invention to discover other "associations" between the "cell penetrating peptide" and the antigen that are appropriately used in making and using the claimed

invention. Given the unpredictable nature of the art and the amount of guidance, direction, and exemplification disclosed, the claimed invention could not be made without undue and unreasonable experimentation.

The claims broadly encompass compositions comprising different types of cells pulsed with a variety of different cell penetrating peptides, which were known in the art at the time the application was filed, disclosing that such compositions are useful for stimulating an immune response against an antigen attached to the cell penetrating peptide. Trehin et al. (*Eur. J. Biopharm.* 2004 Sep; **58** (2): 209-223) has reviewed the state of the art of using cell-penetrating peptides for cellular delivery of cargoes, such as drugs and antigens; see entire document (e.g., the abstract). Trehin et al. teaches the art still suffers from limitations and pitfalls, including potential artifacts associated with the experimental techniques used to study such intracellular delivery systems; see, e.g., page 216, column 2, through page 220, column 1. Among those limitations and pitfalls discussed is the errant assumption that cell-penetrating peptides, such as the Tat-derived cell-penetrating peptides are capable of passing through cell membranes regardless of cell type (page 218, column 2). Rather than accepting, as a general concept, the promiscuity of any given cell-penetrating peptide, Trehin et al. teaches that recent experimentation has illustrated the need to determine on case-by-case basis whether the cell-penetrating peptide is capable of passing through the cell membrane of the targeted cell type (page 218, column 2). Thus, Trehin et al. suggests that the claimed invention cannot be used without undue and unreasonable experimentation, since it would be necessary to determine whether a cell-penetrating peptide is capable of transducing the antigen across the membrane of the "immune effector cell". In not, the compositions encompassed by the claims cannot be expected to be used effectively to stimulate an immune response. Overall, Trehin et al. cautions that a more complete understanding of the mechanisms involved in the translocation of cell-penetrating peptides through cell membranes is still needed, together with more information about the biological limits of their usage, before approaching a meaningful preclinical stage of investigation that may lead to the development of technologies suitable for clinical use (page 220, column 1).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

17. Claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a vaccine comprising an immune effector cell and a cell penetrating peptide, wherein the cell penetrating peptide is associated with an antigen.

Again, the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Consideration of these factors, as expounded below, indicates the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The Nature of the Invention:

Giving the claims their broadest reasonable interpretation in light of the supporting disclosure, which is consistent with that disclosure and consistent with the interpretation that those skilled in the art would reach, the claims are drawn to a composition for preventing and/or treating the onset of disease and/or its progression by stimulating an immune response against an antigen associated with the disease.

Support for this interpretation of the claims is found, for example, at page 30, paragraph {080], where it is disclosed that the invention is useful for preventing or inhibiting the progression of cancer.

The State of the Prior Art:

The art of preventing the incidence and progression of disease by vaccination is an immature art. While it is indeed plausible, if not proven possible to prevent some diseases (e.g., small pox) by vaccination, most diseases cannot be prevented by such means. In particular, the prevention of the onset and progression of cancer is intractable, since unlike viral diseases, such as small pox, the genesis of cancer and its metastatic progression has been associated with many different genetic events stemming, for example, from exposure to carcinogens or spontaneous mutation; and the many different causes of cancer and its progression have not yet been fully established or characterized, and are not understood. Because the causes of the onset and progression of cancer are not fully established, characterized and understood, their prevention by, for example, stimulating an immune response directed against developing or existing cancer cells was, at the time this application was filed, not practical. The amount of guidance, direction and exemplification set forth in the instant disclosure would not satisfactorily remedy this impracticality so as to enable the skilled artisan to use the claimed invention to prevent diseases such as cancer.

The intractability of preventing the progression of cancer is supported by disclosures in the instant specification. For example, at page 45, paragraph [0128], the specification discloses that although the administration to mice of the exemplified composition reduced the number of lung metastases that formed in the mice, the immune response elicited was not sufficient to prevent their formation.

With regard to antitumor immunotherapy, Bodey et al. (*Anticancer Research* **20**: 2665-2676, 2000) teach, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comment, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research"

(page 2668, column 2). Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculate upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). More recently, Bodey et al. (cited *supra*) states, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director

of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. The specification must enable one of skill in the art to make and to use the invention successfully without a need to first perform an undue amount of additional experimentation. To have success, the use of the invention must elicit a cancer-specific CTL response against the polypeptide of SEQ ID NO: 14 or a variant thereof. Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such cases, active specific immunization will be fruitless, since anergic TCL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2).

There is considerable art indicating that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols*. Lee et al. (*Journal of Immunology.* 1999; **163**: 6292-6300) teaches, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee et al. teaches that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee et al. discloses, "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases,

this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee et al. suggest, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee et al. catalogs a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee et al. reports, "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee et al. summarizes their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee et al. refers specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to any of the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by any protocol that uses the claimed invention, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks et al. (*Cancer Research.* 1998; **58**: 4902-4908) teaches that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks et al. discloses that their experience is not unique (page 4907, column 2). Gao et al. (*Journal of Immunotherapy.* 2000; **23**: 643-653) found that although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao et al. teaches that the lack of regression was associated

with a lack of CTL migration to the tumor sites (abstract). Thus, activation of peptide epitope-specific CTL is not an appropriate endpoint and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Since much of the guidance, direction and exemplification provided in this instance is most relevant to the prevention and treatment of melanoma by vaccination, it is further noted that Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290), reviewing the state of the art of T-cell-directed cancer vaccines for treatment of melanoma, states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunisation can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

Summarizing reasons for the lack of successful application of immunotherapy, Bodey et al. teaches that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's

> immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

Regarding the use of cell-penetrating peptides for clinically relevant delivery of cargoes, such as drugs and immunogens, as explained above in the rejection of claims 1-17 under 35 U.S.C. § 112, first paragraph, as lacking a sufficiently enabling disclosure, Trehin et al. (cited supra) has reviewed the state of the art. Overall, given the known limitations and pitfalls, Trehin et al. cautions that a more complete understanding of the mechanisms involved in the translocation of cell-penetrating peptides through cell membranes is still needed, together with more information about the biological limits of their usage, before approaching a meaningful preclinical stage of investigation that may lead to the development of technologies suitable for clinical use (page 220, column 1).

The Relative Skill of those in the Art:

Although high, the relative skill of those in the art is such that, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation would need be performed before the claimed invention, commensurate in scope with the claims, could be made and used to prevent or treat a disease, including cancer, and more particularly melanoma.

The Amount of Direction or Guidance Disclosed in the Specification:

The specification describes the genus of "cell penetrating peptides" to which the claims are directed as peptides capable of transducing another polypeptide into a cell *in vitro* and/or *in vivo*; see, e.g., page 8, paragraph [0029]. The specification discloses that such "cell penetrating peptides" include HIV Tat, HSV VP22, fibroblast growth factor, and the peptides consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 14. However, the specification does not teach the structural features that particularly identify the members of this genus of peptides and

polypeptides, which are capable of transducing another protein into a cell, nor does it teach how such peptides, apart from those actually described in detail, are made.

The specification describes a number of antigens (polypeptides and peptide fragments thereof) that are associated with different types of cancer; see, e.g., page 13-22, Tables 1-5. However, the specification does not appear to describe antigens associated with other diseases; also, it does not appear to describe antigens associated with every type of cancer.

Otherwise, the specification provides only a cursory review of the methodology that might be used to make and use the claimed invention, which does not extend beyond the conventional knowledge of the skilled artisan.

The Presence or Absence of Working Examples:

The specification teaches a composition comprising mature dendritic cells that were pulsed with a synthetic peptide comprising the amino acid sequence set forth as SEQ ID NO: 1 (i.e., the amino acid sequence of the peptide designated "CPP1") and the amino acid sequence of an antigenic fragment of the tumor antigen designated "TRP2" (i.e., the amino acid sequence set forth as SEQ ID NO: 2); see, e.g., page 38, paragraphs [0109] and [0110].

However, as explained in the above rejection of claims 1-17, as lacking a sufficiently enabling disclosure, the specification does not adequately describe the genus of "cell penetrating peptides" to which the claims are directed, or teach methods for making such peptides, so as to permit the skilled artisan to make such peptides without undue and unreasonable experimentation. Again, the specification only provides guidance, direction, and exemplification sufficient to enable the skilled artisan to make the claimed vaccines comprising immune effector cells pulsed with a protein comprising a peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 14, wherein said peptide is covalently linked to an antigenic peptide, as opposed to a vaccine comprising an immune effector cell and a cell penetrating peptide, which is associated with an antigen.

The specification teaches administering the exemplified composition to mice bearing pre-existing, established tumors caused by inoculating the mice with B16 melanoma cells; however, the specification does not teach using the composition to prevent tumor formation by administering the composition before such tumors form. Accordingly, the use of claimed vaccine to prevent the onset or incidence of disease, such as cancer has not been exemplified.

Furthermore, while the specification teaches administering the exemplified composition to mice to elicit an immune response in the mice reduced the number of lung metastases that formed in the mice, it does not exemplify the use of the claimed invention to prevent the progression of the disease and in fact, discloses that the exemplified composition did not do so; see, e.g., page 45, paragraph [0128].

While the specification exemplifies the use of a composition suitable for use in treating mice affected by melanoma, it does not exemplify the use of the claimed invention to treat or prevent any other type of cancer, or any other type of disease.

The specification does not exemplify the successful use of a composition comprising immune effector cells other than mature dendritic cells, as it teaches that other immune cells, such as immature dendritic cells and those of the spleen were not used effectively to stimulate an immune response against melanoma cells expressing the tumor antigen designated "TRP2"; as immunization with spleen cells pulsed with "CPP1-TRP2" did not inhibit tumor growth in the mice; see, e.g., page 45, paragraph [0127]; and Figure 3.

The specification does not exemplify the successful use of a composition comprising "immune effector cells" and a "cell penetrating peptide", which is merely *associated* with an antigen, as opposed to a "cell penetrating peptide" that is covalently linked to the antigen by a peptide bond. In fact, the specification teaches that only a synthetic peptide comprising the amino acid sequence of both the "cell penetrating peptide" (i.e., "CPP1", or the peptide of SEQ ID NO: 1) and the amino acid sequence of an antigenic fragment of the tumor antigen designated "TRP2" (i.e., the amino acid sequence set forth as SEQ ID NO: 2) elicited an immune response in mice that reduced the number of lung metastases in the mice; see, e.g., page 45, paragraph [0127]. A

composition comprising mature dendritic cells pulsed with "CPP1" and the "TRP2 peptide" did not elicit any antitumor immunity, which the specification discloses indicates that a physical link (i.e., a peptide bond) between "CPP1" and the "TRP2 peptide" is required to carry the antigen into the dendritic cells and to subsequently lead to the generation of potent antitumor immunity (page 45, paragraph [0127]).

The Predictability or Unpredictability of the Art:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, the art is characterized by high level of complexity, as well as unpredictability.

Moreover, as the claims are drawn to a genus of structurally varying peptides and polypeptides, it is noted that when comparing the function of two such peptides or polypeptides, with each and every discrepant amino acid residue, the predictability that one will function similarly or identically to the other declines significantly. Even a single alteration in the amino acid sequence a protein can drastically alter both the structure and function of the variant. Burgess et al. (*Journal of Cell Biology*. 1990; **111**: 2129-2138), for example, exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

Regarding the possibility that the claimed invention might be prophylactically or therapeutically useful, the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents

to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

The lack of predictability in the using animal models to determine the effects of administering therapeutic agents in humans is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of such animal models; see entire document (e.g., page 840, column 2).

Shul (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Shul discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1).

Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

The poor extrapolation of the results of treating mice to predict the effects of treating humans is in part due to differences in the immune systems of mice and humans. The significance of these differences is illustrated in the finding that even among different mouse models, successful stimulation of an antitumor immune response in one mouse cannot predict the effect of immunizing another mouse. Kircheis et al. (*Cancer Gene Ther.* 2000 Jun; **7** (6): 870-878), for example, teaches, while allogenic vaccination was effective in one model, it was not effective in another; see entire document (e.g., the abstract).

Finally, to the extent that the claims are drawn to the use of different immunogenic fragments of the various disclosed tumor antigens identified in the specification, only certain immunogenic fragments might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill target cells; other immunogenic fragments will not be effective. Lu et al. (*Cancer Research.* 2002; **62**: 5807-5812), for example, teaches that four of five immunogenic fragments of prostate-specific membrane antigen (PSMA) were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see, e.g., the abstract. These results are reminiscent of the teachings of Lee et al. (cited *supra*) and Zaks et al. (cited *supra*). Thus, while some immunogenic fragments may effective to stimulate a CTL-mediated response to the immunogenic fragment, the skilled artisan cannot predict which immunogenic fragments

of the various and different tumor antigens might be used successfully to prevent or treat cancer.

The Breadth of the Claims:

The claims are directed to vaccines comprising a member of a genus of "immune effector cells", which incongruously is described as inclusive of fibroblasts, which are not immune cells and not conventionally described as "effector" cells; accordingly, the claims are reasonably interpreted as if directed to vaccines comprising any type of cell, and notably not just antigen-presenting cells (e.g., dendritic cells, macrophages).

The claims are directed to such vaccines, which further comprise a member of a genus of "cell penetrating peptides", which vary substantially in both structure and function, despite having the common ability to "transduce another protein into a cell *in vitro* and/or *in vivo*".

Inasmuch as the claims are directed to vaccines comprising any member of a genus of "antigens", the claims are directed to compositions that are useful in preventing and/or treating the onset and progression of any disease, and notably not just cancer.

The Quantity of Experimentation Required:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, undue and/or unreasonable experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be made and used by the skilled artisan to prevent or treat the onset or progression of a disease, such as cancer, or more particularly melanoma, in humans. In other words, the skilled artisan cannot readily, that is, by routine experimentation alone, make and use the claimed vaccines.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed

invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 1-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Wang et al. (*Nat. Biotech.* 2002 Feb; **20** (2): 149-154) (of record; cited by Applicant), which as evidenced by PUBMED™ Identification Number 11821860 is prior art.

PUBMED™ Identification Number 11821860 indicates the cited reference was entered into the database and publicly accessible on February 2, 2002; therefore, the cited reference is prior art under § 102(a).

As noted above in the rejection of claims 3 and 4 under 35 U.S.C. § 112, second paragraph, claims 3 and 4 are vague and indefinite since it cannot be determined to what subject matter the term "T-cell peptides" refers. For clarity, here, claims 3 and 4 are directed to the composition of claim 1, wherein the antigen is a molecule, such as the "TRP2 peptide" taught by the prior art, which absent a showing of any difference, is deemed the same as a molecule comprising multiple "T-cell peptides" from the same tumor antigen. This interpretation is reasonable given the expectation that the disclosed

"TRP2 peptide" binds more than one T-cell, and so is said to comprise "multiple T-cell peptides".

Wang et al. teaches a composition comprising mature dendritic cells pulsed with a synthetic protein comprising the amino acid sequence of a "cell penetrating peptide" and an antigen; see entire document (e.g., the abstract). Wang et al. teaches the amino acid sequence of the "cell penetrating peptide" is that of a peptide designated "CPP1"; see, e.g., page 153, column 1. Wang et al. teaches the antigen (i.e., the "TRP2 peptide") is derived from a tumor antigen designated "TRP2"; see, e.g., the abstract. The amino acid sequences of "CPP1" and the "TRP2 peptide" are covalently bonded, since the synthetic peptide comprises both amino acid sequences adjoined in a contiguous fashion. Wang et al. teaches the "TRP2 peptide" is HLA-A2-restricted (page 149, column 2); therefore, this antigen comprises at least one MNC class I-restricted epitope. Wang et al. discloses that the punctuate pattern of immunofluorescence detected in the experiments performed suggests that the synthetic proteins of which the disclosed composition is composed is intracellularly localized in vesicles such as endosomes, rather than free in the cytoplasm (page 150, column 2).

20. Claims 1-10 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al. (*J. Immunol.* 1997; **159**: 1666-1668), as evidenced by Moy et al. (*Mol. Biotechnol.* 1996 Oct; **6** (2): 105-113).

Here, claims 3 and 4 are directed to the composition of claim 1, wherein the antigen is a molecule, such chemical conjugate disclosed by the prior art, which comprises multiple "OVA peptides" covalently linked to "HIV Tat peptide", which absent a showing of any difference, is deemed the same as a molecule comprising multiple "T-cell peptides" from the same tumor antigen.

Kim et al. teaches a composition comprising dendritic cells pulsed with a antigenic molecule comprising a "cell-penetrating peptide" and multiple "T-cell peptides"; see entire document (e.g., the abstract). Kim et al. teaches the "cell-penetrating peptide" is derived from HIV Tat; see, e.g., page 1666, column 1. Kim et al. teaches the antigenic peptide is a peptide designated "OVA"; see, for example, page 1666, column

1. Kim et al. teaches the dendritic cells processed and presented the peptides in association with MHC class I molecules and stimulated antigen-specific CD8+ T cells in vitro and in vivo; see, e.g., the abstract. Therefore, the antigen comprises at least one MHC class I-restricted peptide.

Although Kim et al. does not explicitly refer to the antigenic peptide "OVA" as a "tumor rejection antigen" or "tumor associated antigen", or more simply a "tumor antigen", Kim et al. teaches the antigen is associated with the tumor cell line EG.7, since antigen-specific T cells primed with the disclosed composition killed those tumor cells (see, e.g., page 1668, Figure 3). As evidenced by Moy et al., the tumor cell line EG.7 was derived from the tumor cell line EL-4 by transducing EL4 cells with the ovalbumin gene (see, e.g., page 106, paragraph bridging columns). Since Kim et al. teaches the tumor cell line EG.7 was killed by the cytotoxic T cells primed using the disclosed composition, absent a showing of any difference, the disclosed composition is deemed the same as the claimed composition comprising a "tumor antigen".

Although Kim et al. does not expressly teach that the dendritic cells of which the disclosed composition was composed were "mature dendritic cells", Kim et al. teaches the dendritic cells were "MHC class II^{high}" (paragraph bridging pages 1666 and 1667). According to the instant specification, "mature dendritic cells" are "is defined as dendritic cells that express high level of MHC class II, CD80 (B7.1) and CD86 (B7.2) molecules" (page 9, paragraph [0034]). While Kim et al. does not disclose whether the dendritic cells also expressed high levels of CD80 and CD86, the Office does not have the facilities to determine if the dendritic cells disclosed by the prior art are distinct from the dendritic cells to which the claims are directed. Nevertheless, Kim et al. discloses the dendritic cells effectively stimulated an antigen-specific immune response in mice treated with the disclosed composition (see, e.g., the abstract). Since the specification discloses that "mature dendritic cells" can be used effectively to stimulate such antigen-specific immune responses in mice, while "immature dendritic cells" cannot (see, e.g., Figure 3), it would appear that the dendritic cells of which the composition of the prior art was composed were necessarily "mature", as opposed to "immature". Therefore, absent a showing of any difference, the dendritic cells disclosed by the prior art are

reasonably deemed the same as the "mature dendritic cells" to which the claims are directed.

Although Kim et al. does not expressly teach that the antigen of which the disclosed composition was composed is housed within a vesicle, or more particularly an endosome in the dendritic cell, as evidenced by Moy et al., such antigens, which are conjugated to the "Tat peptide" are endocytosed and localized in distinct cytoplasmic punctuate vesicles in the cells treated with the conjugated antigens (see, e.g., page 108, column 1). Therefore, absent a showing of any difference, the composition disclosed by Kim et al. is reasonably deemed the same as the compositions to which claims 16 and 17 are directed.

Notably, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed invention differs from than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

21. Claims 1-10, 12, 13, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Application Publication No. 2004/0002455 A1, as evidenced by Wang et al. (*Nat. Biotech*. 2002 Feb; **20** (2): 149-154) (of record; cited by Applicant) and/or Moy et al. (*Mol. Biotechnol.* 1996 Oct; **6** (2): 105-113).

Here, claims 3 and 4 are directed to the composition of claim 1, wherein the antigen is a molecule that comprises multiple "T-cell peptides" derived from the same or different antigens, as it binds to multiple T-cells. Alternatively, the claims are directed to an antigen that is a molecule comprising the amino acid sequences of different peptides derived from the same or different tumor antigens. Again, either interpretation is reasonable given the ambiguity of the claims, as explained above in the rejection under 35 U.S.C. § 112, second paragraph.

U.S. Patent Application Publication No. 2004/0002455 A1 (Uger et al.) teaches a composition comprising dendritic cells loaded (i.e., pulsed) with an antigenic peptide (i.e., an immunogen) attached to a "cell-penetrating peptide"; see entire document (e.g.,

claim 20). Uger et al. teaches the "cell-penetrating peptide" is, for example, a peptide comprising "a transduction sequence" of HSV VP22; see, e.g., paragraph [0016]. Uger et al. teaches the antigenic peptide is, for example, derived from the tumor antigen designated NY-ESO-1; see, e.g., paragraph [0018]. Uger et al. teaches the dendritic cells are "mature"; see, e.g., paragraph [0071]. Uger et al. teaches many peptides derived from different exemplary tumor antigens, which are MHC class I- or class II-restricted; see, e.g., paragraphs [0015], [0019], [0066], and [0067]. Uger et al. teaches the antigen peptide comprises an MHC class I-restricted peptide and a T helper peptide (i.e., a MHC class II-restricted peptide); see, e.g., paragraph [0067]). Uger teaches the antigenic peptide is used in combination with other antigenic peptides in the same composition; see, e.g., paragraph [0018].

Uger et al. does not expressly teach that the antigenic protein of which the disclosed compositions are composed are housed intracellularly in vesicles, or more particularly in endosomes in the antigen-presenting cells (i.e., dendritic cells). Nevertheless, as evidenced by Wang et al. and/or Moy et al., antigenic proteins comprising cell-penetrating peptides, such as those disclosed by Uger et al., are found in the endosomes in the dendritic cells, as further explained in the art rejections above. Therefore, absent a showing of any difference, the compositons disclosed by the prior art are deemed the same as the compositions to which claims 16 and 17 are directed.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
October 25, 2005

Notice to Comply	Application No.	Applicant(s)	
	10/077,555	WANG, RONG-FU	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency, Applicant must provide substitute copies of the Sequence Listing together with an amendment directing its entry and a statement that both copies are the same and include no new matter, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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